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Risks and benefits of commonly used herbal medicines in Mexico

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Abstract

In Mexico, local empirical knowledge about medicinal properties of plants is the basis for their use as home remedies. It is generally accepted by many people in Mexico and elsewhere in the world that beneficial medicinal effects can be obtained by ingesting plant products. In this review, we focus on the potential pharmacologic bases for herbal plant efficacy, but we also raise concerns about the safety of these agents, which have not been fully assessed. Although numerous randomized clinical trials of herbal medicines have been published and systematic reviews and meta-analyses of these studies are available, generalizations about the efficacy and safety of herbal medicines are clearly not possible. Recent publications have also highlighted the unintended consequences of herbal product use, including morbidity and mortality. It has been found that many phytochemicals have pharmacokinetic or pharmacodynamic interactions with drugs. The present review is limited to some herbal medicines that are native or cultivated in Mexico and that have significant use. We discuss the cultural uses, phytochemistry, pharmacological, and toxicological properties of the following plant species: nopal (*Opuntia ficus*), peppermint (*Mentha piperita*), chaparral (*Larrea divaricata*), dandlion (*Taraxacum officinale*), mullein (*Verbascum densiflorum*), chamomile (*Matricaria recutita*), nettle or stinging nettle (*Urtica dioica*), passionflower (*Passiflora incarnata*), linden flower (*Tilia europea*), and aloe (*Aloe vera*). We conclude that our knowledge of the therapeutic benefits and risks of some herbal medicines used in Mexico is still limited and efforts to elucidate them should be intensified.

Keywords: Mexico; Herbal medicine; Pharmacognosy; Ethnopharmacy; Risk of phytomedicine

Introduction

The clinical pharmacologic interest in the efficacy and safety of herbal remedies has grown during past years because of the realization that many people self-medicate using these agents. There is a limited knowledge for health care workers (such as doctors, pharmacists, nurses, and social workers) about the pharmacology and toxicology for the most commonly used herbal remedies in their patients. Here we review some of the most widely used Mexican and Mexican American herbal remedies to give medical practitioners some ideas of the possible pharmacological and physiological effects, potential side effects, and drug interactions for common herbal medicines used by their patients. We also examine the literature on the safety of these agents to raise a warning flag whenever potential hazardous risks are possible.

Although many scientific articles have been published on natural products and their diverse effects, each plant species has several different natural constituents, the great majority of which have not been studied. The present review is limited to species grown and used in Mexico such as nopal (*Opuntia ficus*), peppermint (*Mentha piperita*), chaparral (*Larrea divaricata*), dandlion (*Taraxacum officinale*), mullein (*Verbascum densiflorum*), chamomile (*Matricaria recutita*), nettle or stinging nettle (*Urtica dioica*), passionflower (*Passiflora incarnata*), linden flower (*Tilia europea*), and aloe (*Aloe vera*). Based on our experience, these are the most frequent herbal medicines sought

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Table 1
Commonly used herbal remedies in Mexico

Medicinal plant	Popular names	Cultural uses
Nopal *Opuntia ficus indica*; *Opuntia fuliginosa*; *Opuntia hyptiacantha*; *Opuntia lasciacantha*; *Opuntia macrocentra, Opuntia violacea*; *Opuntia megacantha*; *Opuntia puberula*; *Opuntia streptacantha*; *Opuntia cardona*; *Opuntia velutina*	Nopal, Cactus*	Diabetes and others
Peppermint or Mentha *Mentha piperita*; *Mentha*; *lavanduliodora*; *Mentha arvensis*; *Mentha halpocalyx*	Menta*	Gastrointestinal tract ailments and others
Chaparral *Larrea divaricata*; *Larrea tridentata*; *Larrea mexicana*; *Zygophyllum tridentatum*	Gobernadora*, Creosote Bush, Greasewood, Hediondilla, Larreastat	Arthritis and others
Dandelion *Taraxacum officinale*; *Taraxacum vulgare*; *Leontodon taraxacum*; *Taraxacum dens-leonis*	Diente De Leon* Blowball, Cankerwort, Common Dandelion, Dudal, Herba Taraxaci, Lion's Tooth	Hepatic and biliary ailments, viral and bacterial infections, cancer and others
Mullein *Verbascum densiflorum*; *Verbascum phlomides*; *Verbascum thapiforme*; *Verbascum thapsus*	Gordolobo*, Aaron's Rod, Adam's Flannel, American Mullein, Orange Mullein, Rag Paper	Inflammatory ailments in respiratory tract and others
Chamomile *Matricaria recutita, Chamomilla recutita*; *Matricaria chamomilla*	Manzanilla*, Blue Chamomile, Camomilla, Camomille Allemande, Chamomilla, Echte Kamille, Fleur de Camomile	Gastrointestinal tract ailments and others
Nettle or stinging nettle *Urtica dioic*; *Urtica urens*	Ortiga*, Bichu, Common Nettle, Nettle, Ortie, Small Nettle, Urtica, Urticae herba et folium	Genitourinary ailments, nephrolithiasis and others
Passionflower *Passiflora incarnata*	Corona de Cristo*, Flor de Passion, Madre Selva, Passionflower, Passiflore, Passiflorina, Passionaria	Insomnia, and anxiety or nervousness
Linden *Tilia europaea*; *Tilia vulgaris*; *Tilia cordata*; *synonyms Tilia parvifolia*; *Tilia ulmifolia*; *Tilia tomentosa*; *Tilia argentea*; *Tilia platyphyllos*; *Tilia grandifolia*; *Tilia rubra*	Tila*, European Linden, Lime Flower, Lime Tree, Linden Charcoal, Silver Lime, Tiliae Folium, Tiliae Flos	Insomnia and others
Aloe *Aloe vera*; *Aloe barbadensis*; *Aloe indica*; *Aloe africana*; *Aloe arborescens*; *Aloe natalenis, Aloe frutescens*; *Aloe ucriae*; *Aloe ferox*; *Aloe supralaevis*; *Aloe perryi*; *Aloe spicata*	Zabila*, Aloe Vera, Aloe Latex, Aloe Perfoliata, Burn Plant, Elephant's Gall, Gvarapatha, Gvar Patha, Indian Aloe, and others	Gastrointestinal ailments, wound healing and others

Data from: De Smet (2002), Heinrich (2003), and Federici et al. (2005).
*Popular names in Mexico.

by people who have health problems. Many of these plants have no popular name that is consistently used in English; in other cases the English name may refer to two or more botanically distinct species (see Table 1). The principal reason for focusing a major review on Mexican herbal medicine is the enormous importance of the plants in the popular medicine of Mexicans and Mexican Americans in the United States. Presently, there are few studies which combine a phytochemical and a detailed pharmacological approach (Heinrich, 2003) or studies which systematically explore the risk and benefits of plants. It is not possible at this point to list all the traditional herbal remedies used in Mexico.

Pharmacognosy

According to traditional Mexican medicine, there are diverse healing strategies, as well as different preferences for the plant parts used for various diseases. It is generally accepted that the beneficial effects of medicinal plants can be obtained from active constituents present in the whole plants, parts of plant (as flowers, fruits, roots or leaves), or plant materials or combinations thereof, whether in crude or processed state (De Smet, 2002) (see Table 2).

Many herbalists believe that isolated ingredients have weaker clinical effects than whole plant extracts, a notion that would obviously require proof in each case. The multiconstituent character of crude herbal medicines can render efficacy testing more complex for purified constituents. However, it is necessary to chemically characterize plants and extracts to determine in preclinical studies the efficacy as well as toxicity and to determine if they have biological activity in human clinical trials.

The concept of several active principle ingredients acting in a synergistic manner in herbal remedies may be somewhat unusual to pharmaceutical scientists who are more accustomed to monotherapy using specific therapeutic agents. An example of this phenomenon may be seen in the Mexican herbal remedies which have different active constituents. There are plants that

contain only one or two constituents as chaparral (nordihydroguaiaretic acid, NDGA) and nopal (fibrous polysaccharide and pectine); however, most herbal remedies are reported to contain between 7–12 constituents.

Potential risks of phytomedicine on health

Although the public and some health care professionals believe that herbal medicines are relatively safe because they are "natural", there are remarkably little data to support this assumption. Recent publications have highlighted the severe consequences from side effects from certain herbal products (Gurib-Fakim, 2006; Bush et al., 2007). Many dangerous and lethal side effects have been reported from the use of herbal products. Most of this information has been obtained from health centers and emergency rooms. These side effects may occur through several different mechanisms, including direct toxic effects of the herbs, effects of contaminants, and interactions with drugs or other herbs.

At the present time, it is easier to determine which herbal remedies might induce direct toxicity, because it is known which chemical compounds are present in these plants and which of these compounds are associated with a number of side effects in a significant fraction of users. Side effects may also occur due to contaminants in herbal products, as heavy metals, including lead, mercury, or arsenic, and other undeclared pharmaceuticals, purposefully and illegally added to the herbs to produce a desired effect (Gagnier et al., 2006). In addition, there exist other factors that might also affect the content of active constituents in the herbal product (as microorganisms, microbial toxins, and genetic factors). It is well known that as plants are sessile, they synthesize a vast array of secondary metabolites as defense mechanisms for protecting themselves against pathogen infections (bacteria, fungi, and viruses). Examples of this kind of risk have been demonstrated for some herbal remedies, including some in this review (Table 3). All contain chemical compounds that are considered potentially toxic and they are cited in the Hazardous Substances Data Bank (National Library of Medicine, Bethesda, MD, January 2002).

Medicinal plants behave as authentic medicines because the chemical substances of which they are formed can have a biological activity in humans. For this reason, their joint administration with "conventional medicines" can produce variations in the magnitude of the effect. This type of interaction, just like those produced between two or more medicines, can produce pharmacokinetic interactions if they affect the processes of absorption, distribution, metabolism and excretion, or exert pharmacodynamic interactions. There are numerous examples in the literature of herbal medicine-drug pharmacokinetic interactions (Maniacal and Wanwimolruk, 2001; Unger and Frank, 2004). One of the most important types of interactions occurs between herbal products and drug metabolizing enzyme systems, particularly the cytochrome P450 (CYP) isoenzymes. This type of interaction has a great importance in the clinical practice if we take into consideration that: (1) CYP isoenzymes metabolize a large number of structurally diverse drugs and chemicals, whether natural or synthetic; (2) there are important genetic polymorphisms in drug disposition in different populations; and (3) the variability in potency and complexity of herbal medicine preparations is difficult to assess.

Pharmacodynamic interactions have not been well-described in the literature. However, according to the pharmacological effects reported, there may be examples where herbal medi-

Table 2
Phytochemistry

Herbal remedy	Part of the plant	Active components
Nopal	Leaves	Fibrous polysaccharide (Fiber) and Pectin Rayburn et al. (1998)
Peppermint	Leaves and oil	Peppermint leaf and oil contain acetaldehyde, amyl alcohol, menthyl esters, limone, pinene, phellandrene, cadinene, pugelone, and dimethyl sulfide; trace constituents include alpha-pinene, sabinene, terpinolene, ocimene, gamma-terpinene, fenchene, alpha- and beta-thujone, citronellol, and other compounds. Nair, 2001; Inoue et al., 2002)
Chaparral	Leaves	NDGA Anesini et al. (2001)
Dandelion	Leaves, flowers, and root	Quercetin, luteolin, luteolin-7-*O*-gluccoside, *p*-hydroxyphenylacetic acid, germacranolide acids, chlorogenic acid, chicoric acid, and monocaffeyltartaric acid, scopoletin, aesculetin, aesculin, cichoriin, arnidiol, and faradiol, caffeic acid, taraxacoside, taraxasterol, inulin, and also have high potassium content (Williams et al., 1996; Hu and Kitts, 2003, 2004; Seo et al., 2005; Trojanova et al., 2004)
Mullein	Leaves, flowers, and root	Mullein contains harpagoside, harpagide, aucubin, hesperidin, verbascoside, saponins, and volatile oils Turker and Camper (2002)
Chamomile	Flowerhead	Quercetin, apigenin, and coumarins, and the essential oils matricin, chamazulene, alpha bisaboloid, and bisaboloid oxides (Szoke et al. (2004)
Nettle or stinging nettle	Ground parts and root	Polysaccharides, vitamin C, carotene, beta-sitosterol and the flavonoids quercetin, rutin, kaempferol, and beta-sitosterol (Newall et al., 1996; Schottner et al., 1997; Konrad et al., 2000)
Passionflower	Ground parts	Flavonoids apigenin, luteolin, quercetin, kaempferol, and vitexin; the harman (harmala) alkaloids identified in passionflower include harmine, harmaline, harmalol, harman, and harmin; other constituents include maltol and ethyl maltol Heinrich (2003)
Linden	Dried leaf, flower, and wood	*p*-Coumaric acid, kaempferol, terpenoid, and quercetin constituents; volatile oils, including citral, citronellal, citronellol, eugenol, and limonene Newall et al. (1996)
Aloe	Gel and latex	Emodin anthrone, dithranol, chrysarobin, carboxypeptidase, magnesium lactate, C-glucosyl chromone, salicylate, and allantoin; aloe latex belongs to the anthraquinone family and contains a tricyclic anthracene nucleus Ni et al. (2004)

Table 3
Ethnopharmacology of commonly used plants in Mexico

Herbal remedy	Clinical trials	Side effects	Drug interactions
Nopal	Diabetes BPH Atherosclerosis. Alcohol hangover (Palevitch et al., 1994; Roman-Ramos et al., 1995; Shapiro and Gong, 2002; Cho et al., 2006)	Diarrhea, nausea, abdominal fullness and headache (De Smet, 2002)	None reported
Peppermint	Barium enema-related colonic spasm; dyspepsia; irritable bowel syndrome (Melzer et al., 2004; Mizuno et al., 2006)	Heartburn, nausea, vomiting, allergic reactions; hepatotoxicity; alterations in levels of testosterone, LH, and FSH (Maniacal and Wanwimolruk, 2001; Akdogan et al., 2004; Unger and Frank, 2004)	Cytochrome P450 Maniacal and Wanwimolruk (2001)
Chaparral	None reported	Hepatotoxicity (Kauma et al., 2004)	None reported
Dandelion	Urinary tract infections Anti-inflammatory effect (Cho et al., 2002; Hu and Kitts, 2003)	Allergic reactions, palpitations, syncope and erythema multiforme (Agarwal et al., 2006; Gagnier et al., 2006)	Ciprofloxacine Citochrome P450, UDP-glucoronosyltransferase (Zhu et al., 1999; Maniacal and Wanwimolruk, 2001)
Mullein	Otitis media (De Smet (2002)	None reported	None reported
Chamomile	Dyspepsia Oral mucositis (Melzer et al., 2004; McKay and Blumberg, 2006)	Allergic reactions and conjunctivitis (Paulsen, 2002; De Smet, 2002)	Warfarin Citochrome P450 Segal and Pilote (2006)
Nettle	Osteoarthritis BPH Allergic rhinitis (hayfever) (Mittman, 1990; Lopatkin et al., 2005)	Uterine-stimulant effects, it can induce abortion (Heinrich, 2003; Gagnier et al., 2006)	None reported
Passionflower	Generalized anxiety disorder Opiate withdrawal. (Akhondzadeh et al., 2001)	Dizziness, confusion and ataxia; vasculitis; nausea, vomiting, drowsiness, tachycardia; hepatic and pancreatic toxicity (Heinrich, 2003; Ernest, 2006)	None reported
Linden flower	Anxiety Bundesanzeiger (1998)	Allergic reactions Mur et al. (2001)	None reported
Aloe	Psoriasis Hyperlipidemia Diabetes (Syed et al., 1996; Yeh et al., 2003; Langmead et al., 2004)	Hypoglycemia Hypokalemia Decrease platelet aggregation Prolog bleeding time Diarrhea and loss of water and electrolytes (Shaw et al., 1997; De Smet, 2002; Gagnier et al., 2006)	Hypoglycemic drugs Cardiac glycosides (Shaw et al., 1997; Federici et al., 2005; Bush et al., 2007)

cines might produce synergistic effects when they are used along with conventional medicines (e.g., nopal-hypoglicemiant drugs, chaparral-hepatotoxic drugs, dandelion-anti-inflammatory drugs, chamomile-warpharins, nettle-anti-inflammatory drugs, passionflower-anxiolytic drugs, and aloa-laxative drugs).

Herbal remedies are frequently used by pregnant women, but information about their safety during pregnancy and breast-feeding is scarce. In addition to the miscarriage abortifacient risks of several herbs (e.g., nettle, passionflower, and aloe) (De Smet, 2002; Gurib-Fakim, 2006), there are case reports and epidemiologic studies to suggest that certain herbs (e.g., those that are rich in unsaturated pyrrolizidine alkaloids) are associated with embryotoxic or fetotoxic effects.

Ethnopharmacy of individual medicinal plants

Nopal (Opuntia ficus indica)

Nopal is a member of the *Opuntia* genus and is known in the United States as the prickly pear cactus. This popular herbal is consumed largely by persons from Mexican ascendancy. Not surprisingly, most studies evaluating nopal have been conducted in Mexico. Nopal is used for diabetes, hypercholesterolemia, obesity, alcohol-induced hangover, colitis, diarrhea, benign prostatic hypertrophy (BPH), and atherosclerosis. It has been demonstrated that nopal leaves are effective for the treatment of diabetes, atherosclerosis, BPH, and alcohol hangover. Nopal leaves have a high content of fiber and pectin (Rayburn et al., 1998). Throughout history, the benefits of consuming dietary fiber have been recognized. Soluble fibers, including pectins, gums, and mucilages, increase the viscosity of food in the gut, slowing or reducing sugar absorption. The effect of soluble fiber in reducing serum glucose concentrations is a proposed mechanism of action for the herbal hypoglycemic nopal (De Smet, 2002; Yeh et al., 2003). However, fiber content is not the sole mechanism of action, since fasting blood glucose levels are affected.

Preclinical studies in experimental animals have demonstrated that nopal extracts induce a significant decrease of 17.8% in the area under the glucose tolerance curve and a decrease of 18% in the hyperglycemic peak. In a crossover, placebo-controlled human study of eight patients with Type 2

Diabetes, Roman-Ramos et al. (1995) compared serum glucose levels after patients consumed 500 g of broiled nopal stems with crude extracts and a water control. Serum glucose levels using crude raw extracts or water control were not modified. However, the intake of broiled plant stems caused a decrease in serum glucose levels of 48.3±16.2 mg/dL vs. basal levels at 3 h post-ingestion. The authors suggested that heating may be necessary to achieve a hypoglycemic effect. Shapiro and Gong (2002) have demonstrated the benefit of nopal for improvement of hyperlipidemic profiles. It appears that pectin is able to alter hepatic cholesterol metabolism without affecting cholesterol absorption. On the other hand, previous studies suggest that the consumption of powdered prickly pear cactus flowers 500 mg/day for 2–8 months improves symptoms such as urgency and feelings of fullness in the bladder in some patients with BPH (Palevitch et al., 1994). It has also been reported that nopal reduced some specific symptoms of hangover such as nausea, anorexia, and dry mouth, apparently by inhibiting the production of anti-inflammatory mediators and by its antioxidant effects (Cho et al., 2006). Orally, nopal is usually well-tolerated. However, it has been reported that it may cause mild diarrhea, nausea, increased stool volume, increased stool frequency, abdominal fullness, and headache (De Smet, 2002; Federici et al., 2005).

Peppermint (M. piperita)

Peppermint has a long history of safe use, both in medicinal preparations and as a flavoring agent. Peppermint is used as a remedy for the common cold, inflammatory processes of the mouth, pharynx, sinuses, liver, gallbladder and bowel, as well as gastrointestinal tract ailments such as nausea, vomiting, diarrhea, cramps, flatulence, and dyspepsia. Also it is used for headache, morning sickness, and dismenorrhea. Peppermint leaf and oil contain acetaldehyde, amyl alcohol, menthyl esters, limone, pinene, phellandrene, cadinene, pugelone, and dimethyl sulfide. Trace constituents include alpha-pinene, sabinene, terpinolene, ocimene, gamma-terpinene, fenchene, alpha- and beta-thujone, citronellol, and other compounds (Nair, 2001; Inoue et al., 2002).

Peppermint alters the physiology of the gastrointestinal tract and it is used in clinical trials for the treatment of barium enema-related colonic spasm, dyspepsia, and irritable bowel syndrome. In nine studies, 269 healthy subjects or patients underwent exposure to peppermint either by topical intraluminal (stomach or colon) or oral administration. It was found that peppermint produces an inhibition of spontaneous peristaltic activity, reduces total gastrointestinal transit or gastric emptying, decreases the basal tone in the gastrointestinal tract, reduces the slow wave frequency in the esophagi, small intestine, which slows peristaltic movements, and inhibits potassium depolarization-induced responses in the intestine (Mizuno et al., 2006). It was observed that peppermint relaxed the lower esophageal sphincter, and that it was useful as an antispasmodic agent for double-contrast barium meal examination and in patients with dyspepsia (Melzer et al., 2004). Preliminary evidence suggests that the peppermint component, menthol, may protect against herpes simple virus. In addition, menthol was found to have antibacterial activity against *Clostridium sporogenes*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Pseudomona aeruginosa*, *Salmonella pullorum*, *Sataphylococus aureus*, *Streptococus faecalis*, and *Comamonas terrigena* (Schuhmacher et al., 2003).

Several toxic effects have been associated with ingestion of peppermint oil such as heartburn, nausea, vomiting, allergic reactions, flushing, and headache. Peppermint oil, when used in combination with caraway oil, may cause a substernal burning sensation, belching, heartburn, nausea, vomiting, and diarrhea (Bush et al., 2007). Preliminary research suggests that peppermint leaf preparations might be hepatotoxic at high doses (Akdogan et al., 2004). Other preliminary research indicates that peppermint leaf tea might lower testosterone levels and decrease spermatogenesis in male animals, as well as increase FSH and LH levels. Preliminary evidence suggests that peppermint oil might interact with cytochrome P450 isoforms (CYP1A2, CYP2C19, CYP2C9, and CYP3A4) and therefore might modify levels of drugs metabolized by those cytochromes (Maniacal and Wanwimolruk, 2001; Unger and Frank, 2004).

Chaparral (L. divaricata)

Chaparral commonly referred to as “creosote bush” or “greasewood”, grows in deserts and serves as an herbal remedy among Native Americans in the Southwestern United States and Northern Mexico. Chaparral is used in the Mexican traditional medicines for arthritis, bowel cramps, flatulence, colds, and chronic cutaneous disorders. Also it is used for parasitism, bacterial infections (tuberculosis, venereal disease), gastrointestinal (GI) disorders, central nervous system (CNS) disorders, chickenpox, and snakebite pain. However, there are no clinical trials that support those popular uses. On the contrary, as discussed below, there are hundred of reports about its toxicity. Chaparral contains NDGA and a pro-inflammatory compound (Anesini et al., 2001). This plant is well known for its antioxidant properties (Heinrich, 2003; Ernest, 2006). Although chaparral induces apoptosis (cellular death) in tumor cells (Anesini et al., 2001) and has anti-fungal and antiviral activity *in vitro* (Heinrich, 2003; Gagnier et al., 2006), there are no approved clinical uses reported.

Chaparral use has been associated with severe hepatotoxicity. Since 1990, incidents of chaparral-related hepatotoxicity were reported to the FDA in the USA, and all cases were carefully reviewed generating a clearer picture of its hepatotoxic potential. A study of 18 patients revealed that chaparral-associated toxicity varied from mild hepatitis to cirrhosis and fulminant liver failure (Estes et al., 2003; Bush et al., 2007). The predominant pattern of liver damage observed was cholestatic hepatitis with high serum transaminases and elevation of bilirubin and alkaline phosphatase. A minority of patients presented cirrhosis and two patients required transplantation for fulminant hepatic failure. The mechanism of hepatotoxicity is not known definitively. However, one component has gained significant study, NDGA because it has been identified as hepatotoxic agent in mice (Kauma et al., 2004). This component is a lignan present in the leaves and bark of chaparral and

constitutes up to 10% of dry weight. In low and high doses, it inhibits lipoxygenase pathways. One hypothesis is that high concentrations of NGGA inhibit cyclo-oxygenase leading to the production of pro-inflammatory mediators that produce hepatotoxicity (Kauma et al., 2004).

Dandelion (T. officinale)

Dandelion plants are well-known for their use in Mexican and North American folk medicine remedies and home recipes. Although considered by many to be a troublesome weed, it is also acclaimed as a nontoxic herb of special value in traditional Mexican and Chinese medicine for a variety of health benefits (see Table 1). It is used for loss of appetite, dyspepsia, flatulence, gallstones, bile stimulation, laxative, diuretic, circulatory tonic, skin toner, blood tonic, and digestive tonic. It is also used for the treatment of viral and bacterial infections as well as cancer. Dandelion contains quercetin, luteolin, luteolin-7-*O*-gluccoside, *p*-hydroxyphenylacetic acid, germacranolide acids, chlorogenic acid, chicoric acid, monocaffeyltartaric acid, scopoletin, aesculetin, aesculin, cichoriin, arnidiol, faradiol, caffeic acid, taraxacoside, taraxasterol, and large amounts of the polysaccharide, inulin, as well as a high potassium content (Williams et al., 1996; Hu and Kitts, 2003, 2004; Trojanova et al., 2004; Seo et al., 2005).

Dandelion flower extract, particularly the ethyl acetate fraction (EAF), possesses bioactive phytochemicals with the ability to scavenge ROS and prevent DNA from ROS-induced damage *in vitro* (Hu and Kitts, 2003). In particular, luteolin (3-,4-,5,7-hydroxyl-flavone) and luteolin-7-*O*-glucoside (3-,4-,5-hydroxyl-flavone-7-*O*-glucoside) were among the functional compounds in dandelion flower extract that suppressed oxidative stress (Hu and Kitts, 2003). Preliminary data suggest that dandelion might have anti-inflammatory effects as well (Federici et al., 2005). The dandelion constituents, luteolin and luteolin-7-*O*-gluccoside, seem to suppress prostaglandin E2 and nitric oxide production, possibly by suppressing cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (Hu and Kitts, 2004). Recent studies suggest that dandelion root extracts inhibit production of the inflammatory cytokines interleukin IL-6 and tumor necrosis factor (TNF)-alpha, and this agent may have leukotriene-inhibiting activity (Seo et al., 2005). In addition, other constituents of dandelion root water extract improved lipid metabolism and prevented diabetic complications from lipid peroxidation in diabetic rats (Cho et al., 2002). A preliminary report suggests that dandelion root reduces the recurrence rate of urinary tract infections in women (Zaffani et al., 2006).

Products containing dandelion pollen can cause allergic reactions, including anaphylaxis when it is taken orally (McCutcheon and Beatty, 2000). In one report, a 39-year-old obese woman developed palpitations and syncope after taking a weight loss supplement containing a combination of dandelion, bladderwrack, and boldo for 3 weeks. The patient was found to have prolonged QT-interval on her electrocardiogram with frequent episodes of sustained polymorphic ventricular tachycardia (Agarwal et al., 2006). It is not clear whether dandelion, another ingredient, or the combination of ingredients is responsible for this adverse effect. Topically, dandelion can cause contact dermatitis, erythema multiforme, or an anaphylaxis reaction in sensitive individuals (Federici et al., 2005). Zhu et al. (1999) have demonstrated that co-administration of dandelion with ciprofloxacin modifies the bioavailability and disposition of ciprofloxacin in rats. Results indicated that, as compared to control, maximum plasma concentration (*C*max) of ciprofloxacin was significantly lowered by 73%, increased both apparent drug distribution volume (*V*d: 92.0 vs. 30.8 L/kg), and terminal elimination half-life (*t*1/2, 5.71 vs. 1.96 h). These results suggest that dandelion may have clinical implications on the dosing of ciprofloxacin or other quinolone antibiotics. There is preliminary evidence in animals that dandelion might inhibit cytochrome P450 1A2 (CYP1A2) and it might induce UDP-glucuronosyltransferase, a phase II enzyme (Maniacal and Wanwimolruk, 2001; Unger and Frank, 2004). Theoretically, dandelion might increase the clearance of drugs that are UDP-glucuronosyltransferase substrates. Because dandelion contains significant amounts of potassium, concomitant use with potassium-sparing diuretics might increase the risk of hyperkalemia.

Mullein (V. densiflorum)

Verbascum is known as mullein in the United States and gordolobo in Mexico. Its flowers and leaves are used for a wide range of ailments, such as inflammatory ailments in respiratory tract (cough, colds, chills and flu, tuberculosis, bronchitis, pneumonia, asthma, tonsillitis, and tracheitis). Other uses include the treatment of diarrhea, colic, gastrointestinal bleeding, migraines, gout, sleep disorders, kidney disorders, and chronic inflammation, wounds, burns, hemorrhoids, bruises, frostbite, erysipelas, and inflamed mucosa (see Table 1). However, there are no clinical trials that support these popular uses. Mullein contains harpagoside, harpagide, aucubin, hesperidin, verbascoside, saponins, and volatile oils (Turker and Camper, 2002).

At present, there is but a single report in the literature about the clinical use of mullein for otitis media (Gagnier et al., 2006). However, there are reports relating to the effects of mullein *in vitro*. For example, it has been shown that mullein has *in vitro* antiviral activity against influenza, herpes simplex viruses, herpes simplex virus type 1, and also an anti-bacterial activity against *K. pneumoniae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Escherichia coli* (Turker and Camper, 2002). There are no existing reports about the toxicological effects of mullein in either experimental models or in human beings. Given the wide use of mullein as a Mexican traditional medicine, there is a necessity to conduct preclinical and clinical studies with this herbal product.

Chamomile (M. recutita)

Chamomile (*M. recutita*) is one of the most popular single ingredient herbal teas, or tisanes. Chamomile tea, brewed from dried flower heads, is used traditionally for several medicinal purposes as Gastrointestinal tract ailments as flatulence, nervous diarrhea, spasms, colitis, gastritis, and hemorrhoids. Other uses

include nasal mucous membrane inflammation, allergic rhinitis, attention deficit-hyperactivity disorder (ADHD), restlessness, insomnia, dismenorrhea, mastitis, and varicose ulcers (See Table 1). Chamomile contains quercetin, apigenin, coumarins, and the essential oils matricin, chamazulene, alpha bisaboloid, and bisaboloid oxides (Szoke et al., 2004).

Clinical studies have shown that chamomile might be effective for the treatment of dyspepsia and mucositis. Preliminary research suggests that it blocks slow wave activity in the small intestine, which could slow peristaltic movement (Melzer et al., 2004). In a clinical trial of 98 patients receiving local radiation and systemic chemotherapy, chamomile oral rinse prevented mucositis secondary to radiation therapy and some types of chemotherapeutic drugs including asparaginase, cisplatin, cyclophosphamide, daunorubicin, doxorubicin, etoposide, hydroxyurea, mercaptopurine, methotrexate, procarbazine, and vincristine (McKay and Blumberg, 2006). Chamomilla contains flavonoids, which exert benzodiazepine-like activity (Avallone et al., 2000), and also has a phosphodiesterase inhibitory action, which leads to increased cAMP levels (Kuppusamy and Das, 1992). Gomaa et al. (2003) reported the effect of flavonoids present in chamomilla on inhibition of morphine withdrawal *in vitro*. Recently, Kassi et al. (2004) demonstrated that aqueous extracts of chamomile induce osteoblast differentiation and have anti-cancer effects on breast cancer and uterine cancer *cells in vitro* (concentrations of 10–100 μg/mL). They concluded that chamomile extracts produce these effects because it acts as selective estrogen receptor modulator.

Several reports have appeared in the literature about the toxic effects of chamomile. It has been observed that orally chamomile tea can cause allergic reactions including severe hypersensitivity reactions and anaphylaxis in sensitive individuals (Paulsen, 2002). Chamomile tea can also cause an allergic conjunctivitis. Cases of contact dermatitis (but not reactions of type I) were reported following its topical applications (De Smet, 2002; Federici et al., 2005).

It has been suggested that there are important interactions between chamomile and conventional drugs. Although no evidence of a drug–herb interaction between warfarin and chamomile has been documented, there is a theoretical risk because chamomile contains coumarins. Segal and Pilote (2006) have documented a case of a 70-year-old woman who, while being treated with warfarin, was admitted to hospital with multiple internal hemorrhages after having used chamomile products (tea and body lotion) to soothe upper respiratory tract symptoms. Ganzera et al. (2006) have studied the effect of chamomile essential oil and its major constituents on four selected human cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2D6, and CYP3A4) *in vitro*. Crude essential oil showed inhibition of each of the enzymes, with CYP1A2 being more sensitive than the other isoforms. Three constituents of the oil, namely chamazulene (IC50=4.41 μM), *cis*-spiroether (IC50=2.01 μM), and *trans*-spiroether (IC50=0.47 μM) appeared to be potent inhibitors of this enzyme, also being somewhat active towards CYP3A4, CYP2C9, and CYP2D6. Only chamazulene (IC50=1.06 μM) and alpha-bisabolol (IC50=2.18 μM) revealed a significant inhibition of these latter enzymes. As indicated by these *in vitro* data, chamomile preparations contain constituents that inhibit the activities of major human drug metabolizing enzymes. Interactions with drugs whose route of elimination is dependent on these cytochromes (especially CYP1A2) are therefore possible.

Nettle or stinging nettle (U. dioica)

Nettle is the common name for any of the 30–45 species of flowering plants of the genus *Urtica*. The tops of growing nettles are a popular cooked greens in many areas. Some cooks throw away the first water in order to dismiss the stinging compounds, while others retain the water. Nettle has a variety of uses in traditional medicine for genitourinary ailments (nocturia, frequency, dysuria, urinary retention, irritable bladder, and infections), kidney disorders, allergies, diabetes, internal bleeding (including uterine bleeding, epistaxis, and melena), anemia, GI tract ailments (diarrhea and dysentery, and gastric hyperacidity), musculoskeletal aches, osteoarthritis, and alopecia. However, only a few of these uses have scientific bases that support their clinical uses. Nettle contains the follow compounds: polysaccharides, vitamin C and carotene, beta-sitosterol, and the flavonoids quercetin, rutin, kaempferol, and beta-sitosterol (Newall et al., 1996; Schottner et al., 1997; Konrad et al., 2000).

There is preliminary evidence that stinging nettle above ground parts might improve symptoms of allergic rhinitis (Mittman, 1990). There is contradictory evidence about the effectiveness of stinging nettle for symptoms of BPH. In one study, taking a combination product (PRO 160/120, Willmar Schwabe GmbH, Germany) containing a specific extract of stinging nettle (WS 1031) 120 mg plus a specific extract of saw palmetto (WS 1473) 160 mg twice daily for 24 weeks seemed to significantly improve urinary tract symptoms in men with BPH (Lopatkin et al., 2005). In another trial, an herbal product containing stinging nettle root extract 80 mg, saw palmetto lipoidal extract 106 mg, pumpkin seed oil extract 160 mg, lemon bioflavonoid extract 33 mg, and vitamin A (100% as beta-carotene) 190 IU taken three times daily for 6 months did not significantly improve symptoms of BPH (Marks et al., 2000). Nettle seems to have an anti-proliferative effect on prostatic epithelial and stromal cells, which could be a potential mechanism of action in patients with BPH (Durak et al., 2004).

There is evidence that oral or topical use of stinging nettle leaf extract might improve symptoms of pain in patients with osteoarthritis (De Smet, 2002). Some clinicians use stinging nettle leaf extract in combination with conventional nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesics. Evidence suggests that adding stinging nettle might allow for a lower analgesic dose in some patients to be used (Gagnier et al., 2006). Topically, stinging nettle leaf seems to relieve pain and disability in patients with osteoarthritis of the thumb, according to preliminary research (Randall et al., 2000). More evidence is needed to rate stinging nettle for these uses.

There is some data that stinging nettle can decrease blood glucose levels. Bnouham et al. (2003) demonstrated that when administered 30 min before glucose loading, the aqueous

extract of nettle (AEN) (250 mg/kg) showed a strong glucose lowering effect (33±3.4% decrease compared to the control value 1 h after glucose loading). AEN also exerts a hypotensive action in the rat, although it causes vasoconstriction of the aorta via activation of alpha1-adrenergic receptors (Legssyer et al., 2002). AEN has also been associated with possible abortive and uterine-stimulant effects when used orally (Bush et al., 2007).

There are few reports about the toxic effects of nettle. Nettle root can cause gastrointestinal complaints, sweating, and allergic skin reactions (Heinrich, 2003). Nettle juice can sometimes cause diarrhea (De Smet, 2002). Topically, fresh nettle leaves can cause localized rash, itching, stinging, and tongue edema (Federici et al., 2005).

Passionflower (P. incarnata)

Passionflower (*P. incarnata*) is known as a "calming" herb for anxiety or nervousness, insomnia, seizures, and hysteria. It is used in traditional remedies for anxiety or nervousness, generalized anxiety disorder and symptoms of opiate withdrawal, as well as neuralgia, generalized seizures, hysteria, spasmodic asthma, ADHD, palpitations, cardiac rhythm abnormalities, hypertension, burns, hemorrhoids, and menopause. During the early twentieth century, this herb was included in many over-the-counter sedatives and sleep aids (Ernest, 2006). In 1978, the U.S. Food and Drug Administration (FDA) banned these preparations due to a lack of proven effectiveness. Passionflower contains flavonoids apigenin, luteolin, quercetin, kaempferol, and vitexin. The harman (harmala) alkaloids identified in passionflower include harmine, harmaline, harmalol, harman, and harmin. Passionflower also contains maltol and ethyl maltol (Dhawan et al., 2001a,b).

In a double-blind randomized control trial, 32 patients with generalized anxiety disorder were randomized to receive 45 drops of passionflower tincture or 30 mg oxazepam per day. After 4 days of treatment, no significant differences in term of anxiety levels were noted. Patients treated with passionflower reported fewer adverse effects than those receiving the synthetic anxiolytic (Akhondzadeh and Nazirian, 2001). In animal experiments, Soulimani et al. (1997) also reported that the aqueous extract of *P. incarnata* caused a decrease of rearing and locomotion in the staircase apparatus or exploratory test. Recently, Svenningsen et al. (2006) have found that apigenin, an active ingredient of passionflower, binds to central benzodiazepine receptors, possibly causing anxiolytic effects without impairing memory or motor skills. Passionflower liquid extract (60 drops in combination with clonidine 0.8 mg daily) seemed to be significantly better than clonidine alone when used for reducing symptoms such as anxiety, irritability, insomnia, and agitation (Akhondzadeh et al., 2001). However, the combination was not better than clonidine alone for physical symptoms such as tremor and nausea.

Passionflower can cause dizziness, confusion, and ataxia in some patients (Heinrich, 2003; Ernest, 2006). Altered consciousness has been reported with use of a specific herbal product (Relaxir) produced mainly from the fruits of passionflower (De Smet, 2002). There is also a case reported involving a 34-year-old woman who developed severe nausea, vomiting, drowsiness, prolonged QT interval, and episodes of nonsustained ventricular tachycardia, requiring hospitalization for IV hydration and cardiac monitoring following use of therapeutic doses of passionflower (Agarwal et al., 2006). There is some debate about whether passionflower contains cyanogenic glycosides. Several related Passiflora species do contain them, including *Passiflora edulis*, which is associated with liver and pancreas toxicity (Fisher et al., 2000).

Linden flower (T. europea)

Linden is a tall deciduous tree cultivated in Mexico and North America. Traditionally, linden flowers are used to soothe nerves and to treat conditions associated with stress, including anxiety, insomnia, and hysteria. Also, it is used in traditional remedies for, colds, nasal congestion, throat irritation, headaches, sinus headache, and migraine headache. It is used for treatment of palpitations, hypertension, incontinence, hepatitis, colitis, rheumatism, hemorrhage and lower leg abscesses (ulcus cruris), as well as a diuretic and antispasmodic agent. Linden flowers are known to contain considerable amounts of mucilage. Also, they contain *p*-coumaric acid, kaempferol, terpenoid, quercetin constituents, and volatile oils, including citral, citronellal, citronellol, eugenol, and limonene (Newall et al., 1996).

In Germany, linden flower is an official product listed in the *German Pharmacopoeia*, approved in the Commission E monographs, and the tea form is an official product in the German Standard License monographs (Bundesanzeiger, 1998). It is used as a component of common cold and antitussive preparations and also used in urological and sedative drugs (Newall et al., 1996; Heinrich, 2003). In German pediatric medicine, it is used as a diaphoretic component of an influenza tea for children comprised of linden flower, willow bark, meadow-sweet flower, chamomile flower, and bitter orange peel (De Smet, 2002). Recently, it has been reported that linden has an antispasmodic activity *in vitro* (Federici et al., 2005; Ernest, 2006).

Currently, there exists a single report documenting allergic reaction to linden pollen. Exposure to linden pollen can induce IgE-mediated rhinoconjunctivitis and cough, as demonstrated by skin prick test (SPT), conjunctival provocation, and IgE *in vitro* tests (Mur et al., 2001).

Aloe (A. vera)

Aloe vera is a stemless, drought-resisting succulent of the lily family. Traditionally, linden flowers are used for gastrointestinal ailments (ulcerative colitis, ulcers, constipation, colitis, and laxative), musculoskeletal ailments (osteoarthritis, bursitis, and cold sores), diabetes, asthma, radiation-related mucositis, epilepsy, bleeding, amenorrhea, depression, glaucoma, multiple sclerosis, hemorrhoids, varicose veins, burns, wound healing, psoriasis, sunburn, and frostbite. A clear gel obtained from the cells of the inner leaf is the part of the plant used for topical application. Anthraquinones, one of the most important active components, are contained in the bitter yellow sap of the middle leaf layer. Aloe vera contains a wealth of substances that are biologically active, including emodin anthrone, dithranol,

chrysarobin, carboxypeptidase, magnesium lactate, C-glucosyl chromone, salicylate, and allantoin (Ni et al., 2004).

Aloe latex belongs to the anthraquinone family and contains a tricyclic anthracene nucleus (Table 2). The laxative and purgative effects (at high doses) of Aloe vera latex are attributable to anthraquinones. Aloin, barbaloin, aloe-emodin, and aloectic acid, are a few of the anthraquinones contained in the latex layer. The latest and perhaps most exciting component discovered in Aloe vera is a biologically active polysaccharide known as acetylated mannose, or acemannan. Commercial, stabilized gel products may not work as well as the fresh gel, but cold processing is thought to best retain the beneficial properties. The FDA does not regulate labeling of Aloe vera products.

Aloe vera gel has been widely promoted and used by patients for the treatment of a range of inflammatory digestive and skin diseases, including inflammatory bowel disease (Langmead et al., 2004). Although there is, as yet, little scientific evidence in support of its efficacy in these settings, a randomized trial has shown that topical aloe vera gel is superior to placebo in the treatment of plaque psoriasis (Syed et al., 1996). Preliminary evidence suggests that taking one tablespoon (15 mL) of aloe gel daily for 42 days can significantly decrease blood glucose levels in women with type 2 diabetes (Yeh et al., 2003). There is also some evidence that applying aloe extract 0.5% cream 3 times daily increases healing rates compared to aloe gel or placebo. Aloe vera in doses of 10 mL or 20 mL orally daily for 12 weeks can reduce total cholesterol by about 15%, low-density lipoprotein (LDL) cholesterol by about 18%, and triglycerides by about 25% to 30% in patients with hyperlipidemia (Shapiro and Gong, 2002).

It has been suggested that aloe gel might lower blood glucose levels and have additive effects when used with anti-diabetes drugs (Bush et al., 2007). This might increase the risk of hypoglycemia in some patients receiving hypoglycemics. It has been suggested that overuse of aloe increases the risk of adverse effects from the cardiac glycoside drugs due to potassium depletion. Overuse of aloe, along with cardiac glycoside drugs, can increase the risk of toxicity and might potentiate diuretic-induced potassium loss, increasing the risk of hypokalemia (Shaw et al., 1997; De Smet, 2002). There is a case of excessive intraoperative blood loss in a patient who took aloe 4 tablets/day for 2 weeks prior to surgery for hemangioma. Aloe vera inhibits thromboxane A2, and prostaglandins, and thus might decrease platelet aggregation and prolong bleeding time (Yagi et al., 2002). Due to cathartic and laxative effects of aloe, concomitant use with other stimulant laxatives might produce lost of fluid and electrolytes and there is some concern based on anecdotal reports that aloe latex might induce abortion and stimulate menstruation (Federici et al., 2005; Bush et al., 2007).

Comment

Current estimates suggest that in Mexico as in many developing countries, a large proportion of the population relies heavily on traditional practitioners and medicinal plants to meet primary health care needs. Mexican populations have been found to keep their health traditions when they move to the US. Although modern medicine may be available in the US and elsewhere, herbal medicines (phytomedicines) have often maintained popularity for historical and cultural reasons. Few plant species that provide medicinal herbs have been scientifically evaluated for their possible medical applications. Table 3 summarizes the clinical efficacy data for 10 herbal medicines used as examples in this overview. They show that some herbal medicines are efficacious for certain diseases. However, phase I and II studies should be conducted first to determine the safety and efficacy as well as the optimal dose should then be tested in a phase III trial. The challenge now is to ensure that traditional medicines are used properly, and to determine how research and evaluation of traditional medicines should be carried out. Despite its existence and continued use over many centuries, as well as its popularity and extensive use during the last decade, traditional herbal medicines have not been officially recognized in most countries. Consequently, education, training, and research in this area have not received due attention and support. Our knowledge of the potential benefits and risks of herbal medicines used in Mexico and by Hispanic American people in other countries is still limited. Therefore, efforts to elucidate health benefits and risks of herbal medicines should be intensified.

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